REMARKS

Claims 83, 90 and 113 to 161 are pending in the application.

No new matter has been added by the amendments submitted herein, as explained further below.

Claim 83, as it previously read, was rejected under 35 U.S.C. § 112, first paragraph. Claim 83 has been amended to require the presence of a protein which oxidizes all-*trans* retinoic acid at the C4-position of the ß-ionone ring, as suggested in the first paragraph on page 5 of the outstanding Examiner's Report. Applicant believes this meets all concerns raised with respect to this claim under 35 U.S.C. § 112, first paragraph.

Claim 83, as it read previously, was rejected under 35 U.S.C. § 102(b) as being anticipated by each of Duell *et al.* (1992) and Duell *et al.* (1996). Claim 83 has been amended to require a microsomal preparation that includes a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or expressed by a descendent of such a cell. Further the claim requires that the microsomal preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. See, for example, Figure 13(a) of the application as filed.

None of the Duell *et al.* references teaches or suggests a nucleic acid or protein sequence and so cannot be used to obtain a preparation containing the recited recombinant protein. All of the Duell *et al.* references describe expression of a protein in epidermal (skin) cells only and the expression must be induced by exposure of those cells to retinoic acid. This is much different from Applicants'

invention as claimed in this application, which, through the use of transfection, provides expression of a specific protein without the presence of other cytochromes normally present in skin cells. Moreover, induction of biological activity of this protein by retinoic acid is not required in the transfected cells. An advantage of Applicants' invention as claimed is, for example, in the area of screening drugs (page 9, line 26 to line 40 of the application as filed), where certainty of the identity and presence of the protein being targetted is reproducibly provided, absent contaminating proteins and activities normally present in skin cells. None of the preparations of Duell *et al.* can provide this certainty.

Claim 90, rejected along the same lines as claim 83, has been amended to be directed to a microsomal preparation comprising a recombinant protein which hydroxylates all-*trans* retinoic acid at the C4-position and also requires that the preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. For the reasons that Applicants believe that claim 83 is patentable over the Duell *et al.* articles and other art of record, Applicants believe that claim 90 is patentable.

Each of independent claims 142 and 150, new in the application, has been drafted to meet the requirements set out in the most recent action. Claim 142 requires the recited protein to oxidize all-*trans* retinoic acid at the C4-position of the ß-ionone ring. Claim 150 requires the recited protein to hydroxylate all-*trans* retinoic acid at the C4-position of the ß-ionone ring. Each claim also requires the recited protein to have a minimum amino acid sequence homology of 60 percent with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32, and that the microsomal preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. Support for these claims can be found, for example, in the third paragraph on page 4 of the application as filed.

The remaining claims, all of which are dependent claims, are being submitted for consideration by the Examiner. These claims recite features described in the application as filed, particularly in the third paragraph on page 4, and at line 6 of page 31. Example 1, on page 17 of the specification, describes BLAST search analyses which revealed less than 30 percent sequence homology between SEQ ID NO:2 (zP450RAI) and other previously known cytochrome P450s. Support for claims 158 to 161 is provided by Examples 6 and 7, and particularly Figures 11(a), 11(b) and 13(a).

Applicants note, as discussed in prior submissions, that the activity of the recited class of protein, and accordingly the claimed microsomal preparation, is not limited to that activity recited in the claims. Referring to Example 3, page 15, lines 10 to 11 of the application, "zP450 expression in COS-1 cells promoted the rapid conversion of RA into both lipid- and aqueous-soluble metabolites." This is evident in Figures 4(a) and 4(b), which are elution profiles of radioactively labelled, lipid-soluble RA metabolites of control and zP450RAI-transfected cells. The profiles clearly demonstrate that zP450RAI produces a significant amount (relative to control) of aqueous soluble metabolites other than (more polar than) RA, 4-OH-RA and 4-oxo-RA. Applicants discuss this in Example 3 (page 15, lines 20 to 23), as follows: "It is possible that the aqueous-soluble radioactivity represents glucuronides of RA metabolites or glucuronides of RA itself. Rapid glucuronidation of 4- and 18-hydroxy-RA in mammalian cell extracts has been reported by others [Wouters, 1992; Takatsuka, 1996]." Applicants thus reasonably expect that a member of the recited class of protein oxidizes the 18-position of the ß-ionone ring as well as the 4-position, and that a said member oxidizes retinol as well as RA (see page 3, lines 23 to 26). In Example 5, Applicants describe on page 17 trials in which the metabolism of radioactively labelled RA by hP450RAI-transfected COS cells was examined.

Results are shown in Figures 10(a), 10(b) and 10(c). All three panels of the figure show radioactive RA-derived metabolites not in the control. hP450RAI produced significant amounts of both aqueous and lipid soluble metabolites. Moreover, at least two unidentified metabolites (i.e., not 4-OH-RA or 4-oxo-RA) were produced. Applicants reasonably believe these to be other retinoid oxidation products. The protein recited in claim 83, for example, thus encompasses a protein that not only oxidizes the C4-position of retinoic acid, but also has other retinoid metabolizing activity.

Applicants make these amendments solely to advance prosecution of this application, and reserve the right to file a continuation or other application as appropriate in order to address otherwise outstanding issues.

Applicants believe that all of the issues addressed in the outstanding Action have been addressed in this response, and thus request allowance of the application.

Note Regarding Representation

The undersigned, an appointed agent of the Applicants, has recently changed firms. The new address and telephone number of the undersigned are indicated below. A change of address of the undersigned is on record with the PTO. A Power of Attorney appointing practitioners under the same PTO Customer Number as the undersigned will be submitted in due course.

In the event that any issue remains, or if the Examiner is disposed to issue an unfavorable final action, the Examiner is invited to telephone the undersigned at (416) 865-8281.

A petition for extension of time for submitting this response, and an authorized Visa Credit Card, Form PTO 2038 accompany this response. Applicants hereby request any further extension of time that may be necessary. Please charge any additional fees which may be required for the papers being filed with this letter to our authorized Visa Credit Card. In the event that charges cannot be made to the authorized credit card, please charge any fee to Deposit Account No. 502651.

Yours very truly,

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Date

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